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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/643,141	08/18/2003	Stephen L. Hutcherson	C01037.70049.US	3287

7590 06/17/2009

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EXAMINER	
GUSSOW, ANNE	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
06/17/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/643,141	HUTCHERSON ET AL.	
	Examiner	Art Unit	
	ANNE M. GUSSOW	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *26-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/20/09, 5/7/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claim 26 has been amended.

2. Claims 26-48 are under examination.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on April 20, 2009 and May 7, 2009 were filed after the mailing date of the first action after an RCE on November 7, 2008. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner and an initialed copy of the IDS is included with the mailing of this office action.

Rejections Withdrawn

4. The rejection of claims 26-48 under 35 U.S.C. 112, first paragraph, as lacking enablement regarding the route of administration of the oligonucleotide is withdrawn in view of applicant's amendment to the claims and arguments.

Objections Maintained

5. The objection to the specification as failing to provide antecedent basis for the phrase "wherein the phosphorothioate oligonucleotide is not antisense" is maintained.

Applicant's arguments filed March 9, 2009 have been carefully considered but are deemed not to be persuasive. The response states that, Applicant has established that the claimed oligonucleotides, apart from their ability to produce antisense effects, can produce a cell-mediated immune response. Furthermore, as stated in Applicant's previous response, the specification teaches that "It has now been found, surprisingly, that oligonucleotide analogs having at least one phosphorothioate bond can induce stimulation of a local immune response. This immunostimutation does not appear to be related to any antisense effect which these oligonucleotide analogs may or may not possess." Applicant had clearly recognized in the specification that the immunostimulatory ability of the claimed oligonucleotides is not related to any antisense effect which these oligonucleotides may or may not possess.

In response to this argument, as set forth in the previous office action applicant's description of the oligonucleotides as claimed is limited to the structure of the molecule, both antisense and not antisense describe structural characteristics of the molecule. The argument presented by applicant describes the function of the molecule as not having an antisense effect. The specification describes the oligonucleotides as being antisense molecules (see page 10 lines 16-18 of the as-filed specification and the previous office action). Thus, the structure of the molecule as disclosed is antisense, but the structure of the molecule as claimed is not antisense. However, the function of the molecule in stimulating an immune response is a non antisense effect.

Therefore after a fresh consideration of the claims and the evidence provided the objection is maintained.

Rejections Maintained

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. The rejection of claims 26-48 under 35 U.S.C. 112, first paragraph, as lacking written description is maintained.

Applicant's arguments filed March 9, 2009 have been carefully considered but they are deemed not to be persuasive. The response states that Applicant has disclosed in the specification several phosphorothioate oligonucleotide analogs and their use in promoting cell mediated and local immune responses apart from their ability to produce antisense effect. For example, ISIS 1082 (Seq ID NO: 2) described in the specification is a 21-mer phosphorothioate oligonucleotide analog targeted to the translation initiation codon for the UL13 gene of Herpes Simplex Virus (HSV). ISIS 1082 is an antisense ODN but the immune stimulatory effects of the ODN observed in the Examples are not antisense specific. Repeated intradermal administration of this oligonucleotide to healthy rats with no HSV infections was shown to elicit a local immune response and resulted in the release of cytokines. Thus, even though the rats were not infected with HSV, the HSV antisense ODN (1082) had an immune stimulatory effect. Similarly, repeated administration of ISIS 2105 (Seq ID NO: 1) designed to inhibit the replication of HPV types 6 and 11, to healthy uninfected rats significantly enhanced the humoral response. Incubation of this oligonucleotide analog or ISIS 1082 with an

uninfected in vitro human skin model derived from neonatal keratinocytes and fibroblasts resulted in a concentration dependent increase of cytokine release. Given the absence of any viral infections in the rats and the skin model used in these studies, these examples demonstrate the ability of the claimed oligonucleotides to induce an immunostimulatory response that is unrelated to any antisense effect. Furthermore, in human clinical trials, intradermal injections of ISIS 2105 to healthy male volunteers induced an immune response that was shown to involve both T-cell and B-cell activation. Thus, the data in the specification established that the claimed oligonucleotides can produce a cell-mediated immune response that is not related to any antisense effect which these oligonucleotides may or may not possess (see response pages 5-6).

In response to this argument, the claims encompass thousands of immunostimulatory oligonucleotides that differ in length, sequence, and structure and which generate an immune response. The claimed molecules have no common core structure and can contain methylated or unmethylated CpGs, be of different lengths, contain different modifications to ether the backbone or the nucleotides, for example. The structures of the immunostimulatory oligonucleotides that generate an immune response are not known and the genus is inclusive to a large variety of subgenera having disparate structures and functions. Applicant's reliance on the phosphorothioate backbone as a common structure and the induction of an immune response as a common function of the molecules is not sufficient (see page 6 of applicant's response). McIntyre (Antisense Research and Development, 1993. cited in Applicant's IDS filed August 18, 2003 and the office action mailed February 27, 2006) teach sequence

specific effects of phosphorothioate analogs. Some phosphorothioate analogs do not elicit nonspecific effects or immune responses. However, other phosphorothioate oligonucleotides elicit a sequence specific response. McIntyre, et al. teach that phosphorothioate oligonucleotides can exert sequence-specific effects in vivo, irrespective of sense and antisense orientation (see page 309, Abstract). Nonspecific binding of phosphorothioate oligonucleotides may elicit a localized immune response but can also lead to cytotoxicity of normal cells. Wu, et al. (Anesthesiology, 2001. as cited in the office action mailed February 27, 2006) teach that phosphorothioates molecules may interact non-specifically with cellular targets, resulting in extensive cellular cytotoxicity (see page 1129). Therefore, upon administration of any phosphorothioate oligonucleotide analog, one could expect a wide variety of responses ranging from no response, a nonspecific cytotoxic response to both diseased and healthy cells, an increase in immune system sensitivity to other foreign antigens, a local immune response that may or may not be beneficial to the host, or a sequence-specific response that may or may not be beneficial to the host. As evidenced by the references, the response due to the administration of a phosphorothioate oligonucleotide analog is sequence dependent.

To provide adequate written description and evidence of possession of a claimed genus, a phosphorothioate oligonucleotide that when administered to a patient elicits an immune response; the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, and structure/function correlation. In this case, the only factor present is

the sequence of three phosphorothioate oligonucleotides analogs. Only one of these SEQ ID NO: 1, also referred to in the specification as ISIS 2105, an antisense phosphorothioate oligonucleotide analog, is administered to patients to elicit a local immune response, see Specification, Examples 9-12. Other than the three sequences SEQ ID NOs: 1, 2, and 3 (see Specification page 12, lines 7-9), only one of which was actually administered and shown to elicit a local immune response, no other sequences are provided that would indicate that Applicants are in possession of the genus of phosphorothioate oligonucleotide analogs that elicit an immune response.

A "representative number of species" means that the species, which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See Enzo Biochem, 323 F.3d at 966, 63 USPQ2d at 1615; Noelle v. Lederman, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir.

2004)(Claims directed to PTFE dental floss with a friction-enhancing coating were not supported by a disclosure of a microcrystalline wax coating where there was no evidence in the disclosure or anywhere else in the record showing applicant conveyed that any other coating was suitable for a PTFE dental floss.).

It has been well known that minor structural differences even among structurally related compounds can result in substantially different biology, expression and activities. Based on the instant disclosure one of skill in the art would not know which sequences are essential, which sequences are non-essential and what particular sequence lengths identify essential sequences for inducing an immune response. Mere idea of function is insufficient for written description; isolation and characterization at a minimum are required.

Therefore after a fresh consideration of the claims and the evidence provided the rejection is maintained.

8. The rejection of claims 26-48 under 35 U.S.C. 112, first paragraph, as lacking enablement is maintained.

Applicant's arguments filed March 9, 2009 have been carefully considered but they are deemed not to be persuasive. The response states that the Examiner has repeatedly cited Ratajczak et al. as teaching that the "administration of sequence specific sense, antisense, and control phosphorothioate oligonucleotides to mice result in different responses depending on the sequence administered". (Office Action p. 6) As stated previously, evaluation of splenomegaly and stimulation of B lymphocyte proliferation is one way of measuring a humoral immune response. A cell-mediated

immune response may be evaluated, for instance, by measuring production of inflammatory cytokines such as IL-2, IFNγ, and TNFβ Applicant has demonstrated efficacy of a phosphorothioate oligonucleotide analog in both antibody production and cytokine production. The instant claims are directed to cell-mediated immune responses. The efficacy of the phosphorothioate oligonucleotide analog in eliciting a cell-mediated immune response has been demonstrated in the Examples.
The Examiner has cited Vollmer et al., McCluskie et al. and Jones et al. to demonstrate that administering any phosphorothioate oligonucleotides is unpredictable. Applicant again points out that the results of Vollmer et al. are dosage-specific and that there is an optimal dose for the activity of T-rich nucleic acids which may not be reflected in the data of Vollmer et al. Applicant on the other hand, has demonstrated that several phosphorothioate oligonucleotide analogs (ISIS 2105, 1082 and 2503), apart from their antisense effects, can induce cell mediated responses both in in vitro and in vivo models. Additionally, the fact that some phosphorothioate nucleotide analogs may be less immunostimulatory than other CpG ODNs under certain conditions is not relevant to patentability. At the time of Applicant's invention these post-filing references regarding immunostimulatory motifs were not available to the public. Applicant is only required to show that the claimed method achieves its intended result, and not that it is more successful than other methods. Applicant has met this burden by demonstrating that phosphorothioate nucleotide analogs are immunostimulatory (see response pages 7-8).

In response to this argument, as set forth in the previous office actions, applicant has provided evidence in the specification limited to administration of only one species

of phosphorothioate oligonucleotide, ISIS 2105, which is not sufficient to provide enablement for the entire genus of phosphorothioate analogs. Applicant's arguments regarding Ratajczak, et al. not withstanding, Ratajczak, et al. also examine the effect of phosphorothioate analogs on cell growth and teach that the oligomers had no effect on animal survival or extent of disease (table 1). Since one of the limitations of applicant's claims is wherein the human has cancer (claim 28); administration of an oligonucleotide which has no effect on cell growth would not be supporting of inducing an immune response against the cancer. Further, McCluskie et al (Vaccine, 2001. as cited in the office action mailed February 27, 2006) teaches a polythymidine nucleic acid twenty nucleotides in length (ODN 1983), which did not have an immunostimulatory effect in immunized mice (see page 2658 and Figures 1-2) and Jones et al (Vaccine, 1999. as cited in the office action mailed February 27,2006) teach a T-rich immunostimulatory nucleic acid lacking CpG dinucleotides as a negative control for testing ODNs in vivo for their adjuvant activities in monkeys (see page 3066, right column and page 3067 and Figures 1-2). The specification discloses producing an immune response by administering on one antisense phosphorothioate, ISIS 2105 in rats, mice, and humans. Thus, the data provided is not commensurate in scope with the claims which are drawn to administering a broad genus of analogs comprising thousands of possible structures.

Therefore after a fresh consideration of the claims and the evidence provided the rejection is maintained.

Double Patenting

9. The rejection of claims 26, 28, 29, and 30 as being unpatentable over claims 1-8 of US Patent 6,727,230 (Hutcherson, et al.) in view of US Patent 5356882 (Walker, et al.) is maintained.

The response filed March 9, 2009 has been carefully considered but is deemed not to be persuasive. The response states that applicant's may consider filing a Terminal Disclaimer if some claims are found to be allowable (see response page 11).

In response to this argument, since the claims have not been found to be allowable and a Terminal Disclaimer has not been filed, the rejection is maintained.

Conclusion

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNE M. GUSSOW whose telephone number is (571)272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anne M. Gussow
June 16, 2009

/Anne M Gussow/
Examiner, Art Unit 1643

/David J Blanchard/
Primary Examiner, Art Unit 1643